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**SHORT COMMUNICATION**

# The Difficult Clinical Diagnosis of Erythropoietic Protoporphyria

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## Summary

We give a short survey of the Swedish erythropoietic protoporphyria patients (EPP) with respect to the lapsed time between symptom debut and diagnosis. With two examples we illustrate the consequence of undiagnosed EPP for the patient and also the family. We recall efforts to spread information among health workers in order to investigate patients suffering from extreme sun-exposure intolerance for this uncommon kind of porphyria as well.

**Key words**

Erythropoietic protoporphyria (EPP) • Diagnosis • Protoporphyrin • Sunshine intolerance

Ferrochelatase (FC) deficiency is a genetic defect leading to erythropoietic protoporphyria (EPP). Ferrochelatase, the eighth and final enzyme in the heme biosynthetic pathway, catalyses the incorporation of divalent iron into the protoporphyrin IX molecule (Anderson *et al.* 2001). The genotype in EPP is usually due to the combination of an *FC* gene mutation and a specific low output modulator on the counterpart allele (Gouya *et al.* 2002; Wiman *et al.* 2003). This combination causes a significant reduction of FC-activity which gives rise to accumulation of protoporphyrin in erythrocytes. In the blood vessels, protoporphyrin diffuses out from the erythrocyte and binds to plasma proteins or pass through the capillary endothelium to other cell compartments such as the skin (Todd 1994; Thunell *et al.* 2000). When activated by light within the Soret band this highly photoreactive protoporphyrin provokes an intensive burning pain in the skin. This specific clinical symptom in EPP, together with the presence of the pathognomonic plasma fluorescence peak at 635 nm (Poh-Fitzpatrick and Lamola 1976), makes this porphyria the easiest one to diagnose. Anyhow, three essential factors are needed: a physician that is clinically able to suspect the disorder, a competent laboratory to perform the analysis and provision of the correct kind of sample.

The incidence of EPP in Sweden is about 1:200000 inhabitants (Wiman *et al.* 2003). Porphyria analyses are centralized at the Porphyria Centre Sweden in Stockholm and thus we may assume that virtually all EPP patients in Sweden, with biochemically confirmed EPP diagnosis, are known. On exposure to sun most of the patients have experienced symptoms since early infancy. To our knowledge in none of them the symptoms



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have started at an older age.

The disorder was first clinically described in 1961 (Magnus *et al.* 1961). The first report of EPP families in Sweden was published in 1965 (Haeger-Aronsen and Krook 1965). At present 48 patients have a biochemically confirmed EPP diagnosis (Porphyria Centre Sweden). The genotype in the nine families reported by Wiman et al. 2003 (Wiman *et al.* 2003) and in recently investigated patients is consistent with the genetic pattern mentioned above, i.e. one *FC*-gene mutation combined with the IVS3-48C polymorphism on the counterpart allele, needed for dermatological manifestations.

The mean lapse of time between debut of symptoms and diagnosis is between 10 to 20 years and in one case more than 50 years. In only few cases has the diagnosis been suspected and confirmed in early infancy.

Two examples may illustrate the everyday reality of these patients and their families and the consequences of harbouring the undiagnosed condition:

1) A mother's report:
*When our second son was about two years old our family life changed completely. After few minutes in the sun the boy started to cry and wanted to come inside the house. His cries were so intensive that we trembled each time this happened. This occurred every sunny day. We consulted the paediatric ward on many, many occasions, and his crying was interpreted as due to colic. When he became a little older, outside the house he was always looking for the shadow. When he was five years old a urine sample was collected and sent for investigation. We were informed that "it was negative for porphyria". Under the coming years he was investigated for sun allergy at specialist clinics, without finding any clue to his extreme sunshine intolerance. On several occasions the family was referred to the psychiatric clinic. When he was 10 years, a new sample was taken for porphyria screening, this time a blood sample. The next day we received a telephone call from our son's doctor telling us that he suffered from an uncommon disease, called erythropoietic protoporphyria. "Knowing is, if not all, almost all!" Now we are again a normal family, aware of how to conduct our life in the best way.*

2) A telephone call from a hepatologist at the gastroenterology service in our hospital to the porphyria laboratory:

*We have recently admitted a 50-year-old man with a terminal cholestatic liver failure, for liver transplantation. The cause for the intrahepatic cholestasis is not known in spite of intensive investigations at another hospital. He demands a completely darkened room. He says that since childhood he has been unable to tolerate direct sunshine, and now during these last weeks he cannot even tolerate lamplight. The patient is very silent and gives a depressive impression, which may per se explain his desire to lie in the darkness. My question to you is, can EPP be the reason for this clinical picture?*

Half an hour later the porphyria laboratory calls back to the hepatologist: the diagnosis is with total certainty EPP.

In the child's case, his understanding parents had tried everything to help him, and were convinced that the sun provoked his crying, but they could not guess why and the family situation had been very strained for almost a decade. The 50-year-old man, born before the disease was described and living with adoptive parents had very little chance for a correct diagnosis. He became very silent and lived in the shadow. The progressive cholestasis he developed could not at first be conceived to be due to EPP, and the diagnosis was clear only a few weeks before he died.

Are these extreme cases? Surely not, and efforts should be made to spread information about this extreme sun-sensitive porphyria to general practitioners, paediatricians, dermatologists and other health workers in order to shorten the period before diagnosis. Treatment is symptomatic (Mascaro 1998) and it helps to reduce symptoms during the inevitable minimum exposure to sun. Besides alleviating symptoms, an early diagnosis is of major importance for the affected individual to obtain some kind of legitimacy for his or her suffering (Rufener 1987). For further information on EPP, diagnosis and treatment see the European Porphyria Initiative (EPI) website http://www.porphyria-europe.org/.

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